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(71)Applicant : INOUE NAOYUKI
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(54) ANTI-AIDS VIRUS AGENT

(57)Abstract:
PURPOSE: To reduce the side effect of anti-AIDS virus agent taking advantage of the characteristic sustained release property of microcapsules.
CONSTITUTION: An antiviral agent is added to and uniformly dispersed in a hot solution composed of ethylcellulose-cyclohexane-polyethylene. The dispersion is cooled to deposit ethylcellulose to the circumference of the particle of the antiviral agent and form a coating film of the ethylcellulose. A microencapsulated preparation of the antiviral agent can be prepared by this process. The antiviral agent is selected from among azidothymidine, dideoxycytidine, dideoxyadenosine, dideoxyinosine, foscarnet, etc.

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* NOTICES *

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CLAIMS

[Claim(s)]
[Claim 1] warming which consists of ethyl cellulose cyclohexane polyethylene -- the microencapsulation pharmaceutical preparation of the anti-AIDS virus agent which a solution is made to distribute anti-AIDS virus agents, such as the azidothymidine [AZT] [dideoxycytidine DDC] dideoxy [adenosine DDA] [dideoxyinosine DDI] FOSUKA network, and covers the perimeter with ethyl cellulose and changes

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the microencapsulation pharmaceutical preparation and its manufacture approach of an anti-AIDS virus agent.
[0002]
[Description of the Prior Art] Although the development of the anti-AIDS virus agent to a human immunodeficiency virus [HIV] said to be the pathogen of acquired immune deficiency syndrome [AIDS] attracts attention all over the world, candidates, such as the azidothymidine [AZT] [dideoxycytidine DDC] dideoxy [adenosine DDA] [dideoxyinosine DDI] FOSUKA network, are raised as a remedy for an AIDS virus and various examples of a clinical trial are sent in recent years, the present condition is still that special decide and there is nothing **.
[0003]
[Problem(s) to be Solved by the Invention] The big reason is the point that the side effect at the time of use of an anti-[these] AIDS virus agent is regarded as questionable. It is said that a human immunodeficiency virus [HIV] is infected with the cell of T-four lymphocyte which is a kind of the T cell mainly contained in the lymphocyte in a leucocyte, and plays the commander-role of an immunoreaction, and a macrophage / mono-site system. A human immunodeficiency virus [HIV] is a spherical virus infected considering the T-four lymphocyte as main targets, and when the important thing on the structure combines with the receptor called T four on the front face of a lymphocyte to the sugar protein [glycoprotein] which projects and exists in the film which wraps the perimeter of a human immunodeficiency virus [HIV], virus infection starts. The human immunodeficiency virus [HIV] has a gene with the RNA mold, and although the human immunodeficiency virus [HIV] which invaded into T-four lymphocyte enters in the DNA gene of a cell, it is necessary to transpose own RNA of a virus to DNA [for this to be called a provirus] of a duplex chain using reverse transcriptase then. And hiding out till the day to reactivate, or beginning growth immediately, and using a host cell, the provirus which entered into DNA in the nucleus of a host cell makes protein, such as own gene [RNA] of a virus and film which wraps it, compound, and is left from a host cell. T-four lymphocyte generally made into the host will be destroyed. That is, in order that an operation of an anti-AIDS virus agent may attain to not only a human immunodeficiency virus [HIV] but the normal cell and organ function of the whole body, if it side effects [various] [AZT], for example, azidothymidine, becomes by administration of an anti-AIDS virus agent, hematopoietic injury, such as leukopenia, ischemia or neutrophil leucocyte, and plasma plate reduction, will be caused. In addition, if dideoxyinosine [DDI] has many doses, it is supposed that side effects, such as pancreatitis and peripheral neuropathy, are caused. Moreover, the side effect of peripheral neuropathy is seen by dideoxycytidine [DDC]. Calling it the prime cause must prescribe an anti-AIDS virus agent for the patient over a long period of time, in order that a human immunodeficiency virus [HIV] may infiltrate into intracellular in the form of DNA. When azidothymidine [AZT] is used continuously in relation to this and it continues prescribing a medicine for the patient, it is recognized that it also becomes clear that the appearance of an azidothymidine [AZT] resistance human immunodeficiency virus [HIV] is accepted, and there is a limitation in the independent therapy of current azidothymidine [AZT] from the inside of a patient. Then, the method of prescribing the 2nd selection medicine of an anti-AIDS virus agent for the patient is taken. For example, if the patient to whom the azidothymidine [AZT] resistance human immunodeficiency virus [HIV] appeared is medicated with an anti-AIDS virus agent called dideoxyinosine [DDI] dideoxycytidine [DDC], results that azidothymidine [AZT] susceptibility returns are reported. It is considered to be the best AIDS cure in a present stage to use together two or more anti-AIDS virus agents from this. However, the problem by many side effects that it

was said previously that the chronic administration of an anti-AIDS virus agent is continued arises, the therapy to the side effect must also be performed together with an AIDS therapy, and doing the bad influence to a patient is also considered. Moreover, it also becomes refraining from prescribing for the patient the anti-AIDS virus agent of the considerable amount which can obtain the anti-AIDS virus effectiveness by being apprehensive about such a side effect.

[0004]

[Means for Solving the Problem] Although the drug effect of an anti-AIDS virus agent is wanted to demonstrate uniformly over a long period of time in order to solve these troubles, in the conventional anti-AIDS virus agent, it is not a still solvable problem. Then, this invention offers the microencapsulation pharmaceutical preparation of the anti-AIDS virus agent to which the operation which mitigates the side effect which is the greatest purpose of this invention with the point that drug effect is maintained over the long period of time of an anti-AIDS virus agent, the amount into which an anti-AIDS virus agent flows from pharmaceutical preparation, the point that a rate can be adjusted, etc. is urged.

[0005] The microencapsulation pharmaceutical preparation of the anti-AIDS virus agent in this invention uses naturally-ocurring polymers or synthetic macromolecule for microcapsule wall membrane. A uniform solution is adjusted, after mixing a cyclohexane with ethyl cellulose and polyethylene preferably and warming. Next, it is made to distribute in addition to the solution which had anti-AIDS virus agents, such as the azidothymidine [AZT] [dideoxycytidine DDC] dideoxy [adenosine DDA] [dideoxyinosine DDI] FOSUKA network, adjusted. Next, you stir this mixture and make it cool. The perimeter of the particle of an anti-AIDS virus agent whose giant-molecule ethyl cellulose which serves as wall membrane in the process in which mixture is cooled is the heart matter is piled up, and coat-ization is carried out. The particle of the anti-AIDS virus agent then covered with ethyl cellulose precipitates. Moreover, polyethylene dissociates gradually and begins to float in a broth and the cyclohexane solution upper layer as a process progresses. The cyclohexane solution upper layer which carried out standing neglect after this and contained the separated polyethylene is made to flow out, the organic solvent solution of the surface active agent permitted by the mixed liquor which remained in the living body, and n-hexane solution of a polyoxyethylene hardening castor oil derivative are added, and standing neglect of this is carried out. And the organic solvent solution of a surfactant is added to the mixed liquor which the solution layer was made to flow out again and remained like the first half. When this activity is repeated, the thin film of a surfactant will be made on the front face of the particle of the anti-AIDS virus agent covered with ethyl cellulose. The particle of the covered anti-AIDS virus agent is dried by the approach of arbitration.

[0006] It is possible to use also for the approach of being able to make the microencapsulation pharmaceutical preparation of the anti-AIDS virus agent of this invention obtained as mentioned above mixing in liquids for injection, such as a glucose, water, or physiological sodium chloride solution, and making it pouring in into a blood vessel, or oral administration. In addition, it can be used also for a suppository or ointment.

[0007]

[Example] Ethyl cellulose 0.5g and a polyethylene [molecular-weight 7000 [about]] 0.5g list are made to mix cyclohexane 50ml with 100ml beaker, and it heats to 80 degrees C, and considers as a uniform solution. 2.0g [hiding place thymidine] of anti-AIDS virus agents is added, and homogeneity is distributed. It stirs by rotational frequency 1200rpm with a magnet stirrer. When temperature falls to 25 degrees C, the perimeter of an anti-AIDS virus agent particle is piled up, and ethyl cellulose forms an initial microcapsule, and precipitates in the beaker lower part. Polyethylene serves as a form which begins separation gradually and floats in the cyclohexane liquid upper part then. Let the ethyl cellulose which remains in a beaker using n[in which carried out up cyclohexane laminar-flow appearance, and the polyoxyethylene [60] hardening castor oil derivative [HCO-60 and made in Nikko Chemical] was made to mix 1%]-hexane 50ml which contain polyethylene after that be a coat. And an anti-AIDS virus agent is washed. The microencapsulation pharmaceutical preparation of cyclohexane laminar-flow appearance, HCO-60 addition, and the anti-AIDS virus agent that was able to perform the above 5 times preferably 5 to 10 times is dried by 45-degree C warm air for 6 to 8 hours.

[0008] The microencapsulation pharmaceutical preparation of the anti-AIDS virus agent obtained by the above-mentioned approach is 100-500 micrometers of mean diameters, and it has checked that 18-gage needle and the catheter for angiography were passed. Furthermore, when unevenness is attached to the front face of microencapsulation pharmaceutical preparation and it pours in into a blood vessel, it is possible that that resistance with blood becomes large floats freely within idea ******.

[0009] Measurement at 37 degrees C or less of temperature was tried [30mg of microencapsulation

pharmaceutical preparation of an anti-AIDS virus agent] for the rate of dissolution of the anti-AIDS virus agent hiding place thymidine to the inside of 30ml physiological sodium chloride solution.

[0010] In measurement result standing measurement, it was 30**1.8% [mean**S.D.n=3] in 6 hours. Moreover, by rotation measurement by stirring, internal anti-AIDS virus agent perfect elution took 4 hours. However, the rotational frequency in the case of measurement was set to 5 - 10rpm.

[0011] The artery impregnation to an adult dog was tried as an animal experiment. The thing which the vessel catheter [the bore of 1mm] was inserted [thing] from the crotch artery into the renal artery to the crossbred adult dog [weight of 15kg], and made 50ml physiological sodium chloride solution float 15mg of microencapsulation pharmaceutical preparation of an anti-AIDS virus agent through a catheter was poured in.

[0012] Although the concentration in peripheral blood showed the peak immediately after impregnation, when it is an anti-AIDS virus agent, it can acquire the numeric value of 0.3433**0.0467microg [/ml] anti-AIDS virus agent hiding place thymidine [mean**S.E.n=5]. When it compared with the value of 2.16**0.21microg [n= 3]/ml the case of the conventional dosage forms, the 6 times as many difference as this came out. Saying proves that the direction of microencapsulation pharmaceutical preparation has few outflows out of a kidney compared with administration by the conventional tablet. Moreover, the liver of an adult dog was extracted for the microencapsulation pharmaceutical preparation of anti-AIDS virus agent hiding place thymidine 8 hours after after administration, and when the concentration of the hiding place thymidine in an in-house was measured, the numeric value said in 27.37**10.08microg/ml has been checked. About this, when the same tablet of the former [adult dog] was administered orally and the concentration of the hiding place thymidine in the kidney of 8 hours after was measured, hiding place thymidine was not able to be measured from a kidney in-house. It is proved saying that the microencapsulation pharmaceutical preparation of hiding place thymidine attains to [an operation] long duration compared with the usual tablet and is effective.

[0013] Possibility of the microencapsulation pharmaceutical preparation of the anti-AIDS virus agent which is this invention as above that mitigation of a side effect can be achieved is also high, and its durability of drug effect is also good. The effectiveness different from the chemical treatment method of the conventional HIV infectious disease again is expected.

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(54)【発明の名称】　抗エイズウイルス剤

(57)【要約】　（修正有）

【構成】エチルセルロース・シクロヘキサン・ポリエチレンからなる加温溶液に抗ウィルス剤を加えて均一に分散させた後冷却し、エチルセルロースを抗ウィルス剤粒子の周囲に集積させ、被膜を形成させることによって得られる抗ウィルス剤のマイクロカプセル化製剤。抗ウィルス剤はアジドチミジン、ジデオキシシチジン、ジデオキシアデノシン、ジデオキシイノシン、フオスカネット等から選ばれる。

【効果】マイクロカプセルの特徴である徐放性を生かして、抗エイズウィルス剤の副作用を軽減する目的が有効に達成される。

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【特許請求の範囲】

【請求項１】エチルセルロース・シクロヘキサン・ポリエチレンからなる加温溶液にアジドチミジン〔ＡＺＴ〕ジデオキシシチジン〔ＤＤＣ〕ジデオキシアデノシン〔ＤＤＡ〕ジデオキシイノシン〔ＤＤＩ〕フォスカネット等の抗エイズウイルス剤を分散させ、その周囲をエチルセルロースで被覆して成る、抗エイズウイルス剤のマイクロカプセル化製剤

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は抗エイズウイルス剤のマイクロカプセル化製剤及びその製造方法に関するものである。

【０００２】

【従来の技術】近年、後天性免疫不全症候群〔ＡＩＤＳ〕の病原体であると言われている、ヒト免疫不全ウイルス〔ＨＩＶ〕に対する抗エイズウイルス剤の開発が全世界で注目され、対エイズウイルス治療薬としてアジドチミジン〔ＡＺＴ〕ジデオキシシチジン〔ＤＤＣ〕ジデオキシアデノシン〔ＤＤＡ〕ジデオキシイノシン〔ＤＤＩ〕フォスカネット等の候補があげられ、様々な臨床試験例が出されているが未だにこれといった決めてがないのが現状である。

【０００３】

【発明が解決しようとする課題】その大きな理由はこれら抗エイズウイルス剤の使用時に於ける副作用が問題視されている点である。ヒト免疫不全ウイルス〔ＨＩＶ〕は主に白血球の中のリンパ球に含まれるＴ細胞の一種であり、免疫反応の司令官的役割を果たすＴ$_4$リンパ球とマクロファージ／モノサイト系の細胞に感染すると言われている。ヒト免疫不全ウイルス〔ＨＩＶ〕はそのＴ$_4$リンパ球を主なターゲットとして感染する球状のウイルスで、その構造上で重要なものはヒト免疫不全ウイルス〔ＨＩＶ〕の周囲を包む膜に突出して存在する糖タンパク〔ｇｌｙｃｏｐｒｏｔｅｉｎ〕にリンパ球表面のＴ$_4$とよばれるレセプターと結合することによって、ウイルス感染が始まる。ヒト免疫不全ウイルス〔ＨＩＶ〕は遺伝子をＲＮＡ型で持っており、Ｔ$_4$リンパ球に侵入したヒト免疫不全ウイルス〔ＨＩＶ〕は細胞のＤＮＡ遺伝子内に入り込むが、その時に逆転写酵素を使ってウイルス自身のＲＮＡを二重鎖のＤＮＡ〔これをプロウイルスと呼ぶ〕に置き換える必要がある。そして宿主細胞の核内にあるＤＮＡに入り込んだプロウイルスは再活性化する日まで潜伏するか、すぐに増殖を始めて宿主細胞を利用しながら、ウイルス自身の遺伝子〔ＲＮＡ〕や、それを包む膜等のタンパク質を合成させ、宿主細胞から出ていく。一般に宿主とされたＴ$_4$リンパ球は破壊されてしまう。即ち抗エイズウイルス剤の作用は、ヒト免疫不全ウイルス〔ＨＩＶ〕に限らず全身の正常な細胞及び臓器機能にも及ぶため、抗エイズウイルス剤の投与によって様

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々な副作用、例えばアジドチミジン〔ＡＺＴ〕ならば白血球減少、貧血又は好中球、血漿板減少といった造血障害が引き起こされる。その他ジデオキシイノシン〔ＤＤＩ〕は投与量が多いと膵炎や末梢神経障害等の副作用を起こすとされている。又ジデオキシシチジン〔ＤＤＣ〕にも末梢神経障害の副作用がみられる。その根本的原因と言うのはヒト免疫不全ウイルス〔ＨＩＶ〕はＤＮＡの形で細胞内に潜入するため長期に渡って抗エイズウイルス剤を投与しなければならない。このことに関連して例えばアジドチミジン〔ＡＺＴ〕を連用して投与し続けると患者内よりアジドチミジン〔ＡＺＴ〕耐性ヒト免疫不全ウイルス〔ＨＩＶ〕の出現が認められることも明らかとなり現在アジドチミジン〔ＡＺＴ〕の単独療法には限界のあることが認識されつつある。そこで抗エイズウイルス剤の第２選択薬を投与する方法がとられる。例えばジデオキシイノシン〔ＤＤＩ〕ジデオキシシチジン〔ＤＤＣ〕といった抗エイズウイルス剤をアジドチミジン〔ＡＺＴ〕耐性ヒト免疫不全ウイルス〔ＨＩＶ〕の出現した患者に投与するとアジドチミジン〔ＡＺＴ〕感受性が戻るとの成績が報告されている。このことから複数の抗エイズウイルス剤の併用を実施しているのが現段階に於いて最良のＡＩＤＳ治療法であると考えられる。しかし抗エイズウイルス剤の長期投与を続けていくと先に述べた数々の副作用による問題が生じその副作用に対する治療もＡＩＤＳ治療と合わせて行わなければならず、患者への悪影響を及ぼすことも考えられる。又このような副作用を危惧することによって抗エイズウイルス効果をあげることのできる相当量の抗エイズウイルス剤を投与することを差し控えることにもなる。

【０００４】

【課題を解決するための手段】これらの問題点を解決するためには抗エイズウイルス剤の薬効が長期にわたり一定に発揮することが望まれるが従来の抗エイズウイルス剤ではまだ解決できる問題ではない。そこで本発明は抗エイズウイルス剤の長期にわたって薬効が保たれる点、製剤より抗エイズウイルス剤が流出する量、速度を調整できる点等により本発明の最大の目的である副作用を軽減する作用を促す抗エイズウイルス剤のマイクロカプセル化製剤を提供するものである。

【０００５】本発明に於ける抗エイズウイルス剤のマイクロカプセル化製剤はマイクロカプセル壁膜に天然高分子或いは合成高分子を用いる。好ましくはエチルセルロースとポリエチレンとシクロヘキサンを混合させ加温した後均一な溶液を調整する。次にアジドチミジン〔ＡＺＴ〕ジデオキシシチジン〔ＤＤＣ〕ジデオキシアデノシン〔ＤＤＡ〕ジデオキシイノシン〔ＤＤＩ〕フォスカネット等の抗エイズウイルス剤を調整された溶液に加え分散させる。次にこの混合物を撹拌し冷却せしめる。混合物が冷却される過程に於いて壁膜となる高分子エチルセルロースが芯物質である抗エイズウイルス剤の粒子の周

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囲に集積され皮膜化をさせる。その時エチルセルロースによって被覆された抗エイズウイルス剤の粒子が沈殿する。又工程が進むにつれてポリエチレンが次第に分離しだし、シクロヘキサン溶液上層に浮遊しはじめる。この後静置放置し分離されたポリエチレンを含んだシクロヘキサン溶液上層を流出させ、残った混合液に生体内に許容される界面活性剤の有機溶媒溶液、ポリオキシエチレン硬化ひまし油誘導体のｎ－ヘキサン溶液を加えこれを静置放置する。そして再び液層を流出させ残った混合液に前期と同じように界面活性剤の有機溶媒溶液を加える。この作業を繰り返していくとエチルセルロースによって被覆された抗エイズウイルス剤の粒子の表面に界面活性剤の薄膜がなされることになる。被覆された抗エイズウイルス剤の粒子は任意の方法によって乾燥させる。

【０００６】上記のように得られた本発明の抗エイズウイルス剤のマイクロカプセル化製剤はグルコース、水もしくは生理的食塩水等の注射用液体に混入させることができ、それを血管内に注入させる方法や内服にも用いることが可能である。その他座薬や軟膏にも使用できる。

【０００７】

【実施例】エチルセルロース０．５ｇ、ポリエチレン〔分子量約７０００〕０．５ｇ並びにシクロヘキサン５０ｍｌを１００ｍｌビーカーで混合させ、８０℃まで加熱し均一な溶液とする。抗エイズウイルス剤〔アジトチミジン〕を２．０ｇ加え均一に分散させる。マグネットスターラーにより回転数１２００ｒｐｍで撹拌を行う。２５℃まで温度が下がった時点に於いてエチルセルロースが抗エイズウイルス剤粒子の周囲に集積され、初期マイクロカプセルを形成しビーカー下部に沈殿する。その時ポリエチレンは徐々に分離を始めシクロヘキサン液上部に浮遊する形となる。その後ポリエチレンを含む上部シクロヘキサン層流出させ、ポリオキシエチレン〔６０〕硬化ひまし油誘導体〔ＨＣＯ－６０、日光ケミカル製〕を１％混入させたｎ－ヘキサン５０ｍｌを用いビーカー内に残るエチルセルロースを皮膜とする。そして抗エイズウイルス剤を洗浄する。シクロヘキサン層流出、ＨＣＯ－６０添加、以上を５～１０回、好ましくは５回行い得ることのできた抗エイズウイルス剤のマイクロカプセル化製剤を４５℃の温風で６～８時間乾燥させる。

【０００８】上記方法によって得た抗エイズウイルス剤のマイクロカプセル化製剤は平均粒径１００～５００μｍであり１８－ゲージ針、又血管撮影用カテーテルを通＊

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＊過されるのを確認できた。更にマイクロカプセル化製剤の表面には凸凹が付けられてあり血管内に注入した際に血液との抵抗が大きくなることが考えらわ血液内で自由に浮遊することが考えられる。

【０００９】抗エイズウイルス剤のマイクロカプセル化製剤３０ｍｇを３０ｍｌ生理的食塩水中への抗エイズウイルス剤アジトチミジンの溶出速度を体温３７℃以下での測定を試みた。

【００１０】測定結果

静置測定では６時間で３０±１．８％〔ｍｅａｎ±Ｓ．Ｄ．ｎ＝３〕であった。又撹拌によっての回転測定では、内部抗エイズウイルス剤完全溶出に４時間を要した。ただし測定の際の回転数は５～１０ｒｐｍとした。

【００１１】動物実験として成犬への動脈注入を試みた。雑種の成犬〔体重１５ｋｇ〕に対し股動脈から血管カテーテル〔内径１ｍｍ〕を腎動脈内に挿入しカテーテルを通じて５０ｍｌの生理的食塩水に抗エイズウイルス剤のマイクロカプセル化製剤１５ｍｇ浮遊させたものを注入した。

【００１２】末梢血中濃度は注入直後にピークを示したが抗エイズウイルス剤の時抗エイズウイルス剤アジトチミジン０．３４３３±０．０４６７μｇ／ｍｌ〔ｍｅａｎ±Ｓ．Ｅ．ｎ＝５〕の数値を得ることができる。従来の剤形の場合２．１６±０．２１μｇ／ｍｌ〔ｎ＝３〕の値と比較した場合６倍の違いがでた。と言うことは従来の錠剤による投与に比べマイクロカプセル化製剤の方は腎外への流出が少ないことを証明している。又、抗エイズウイルス剤アジトチミジンのマイクロカプセル化製剤を投与後８時間後に成犬の肝臓を摘出し、組織内に於けるアジトチミジンの濃度を測定したところ２７．３７±１０．０８μｇ／ｍｌと言う数値が確認できた。このことについて、同じく成犬に従来の錠剤を経口投与したばあいも８時間後の腎臓に於けるアジトチミジンの濃度を測定したところ、腎組織内からはアジトチミジンを測定することができなかった。ということはアジトチミジンのマイクロカプセル化製剤が、通常の錠剤に比べ作用が長時間に及んで有効であることが立証されている。

【００１３】以上のとおり本発明である抗エイズウイルス剤のマイクロカプセル化製剤は副作用の軽減を果たせる可能性も高く、又薬効の持続性も良好である。従来のＨＩＶ感染症の化学治療法と又違った効果が期待される。

フロントページの続き

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